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AMRL-TDR-63-44

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THERAPY OF ACUTE UDMH INTOXICATION

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TECHNICAL DOCUMENTARY REPORT No. AMRL-TDR-63-44

JUNE 1963

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6570th AEROSPACE MEDICAL RESEARCH LABORATORIES
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

20060707081

Project No. 6302, Task No. 620202

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<p>Aerospace Medical Division, 6570th Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio. Rpt. No. AMRL-TDR-63-44. THERAPY OF ACUTE UDMH INTOXICATION. Final report, Jun 63, iii + 8 pp. incl. illus., tables, 10 refs. Unclassified report</p> <p>The potentially toxic agent, 1,1-dimethylhydrazine (UDMH), has become very important from a medical viewpoint because of its large-scale use as a missile propellant. Pharmacological studies have revealed that the compound is primarily a central nervous system irritant, and latently causes cardiovascular collapse and ensuing irreversible shock. Pyridoxine therapy constitutes the first successful approach to</p> <p>(over)</p>	<p>UNCLASSIFIED</p> <ol style="list-style-type: none"> 1. Methyl Hydrazines 2. Toxicology 3. Vitamin B 4. Primates 5. Rodents 6. Dogs <ol style="list-style-type: none"> I. AFSC Project 6302, Task 630202 II. Biomedical Laboratory III. Back, K. C. IV. Pinkerton, Mildred K. V. Thomas, A.A. IV. In DDC collection V. Aval fr OTS: \$0.50 <p>UNCLASSIFIED</p>	<p>Aerospace Medical Division, 6570th Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio. Rpt. No. AMRL-TDR-63-44. THERAPY OF ACUTE UDMH INTOXICATION. Final report, Jun 63, iii + 8 pp. incl. illus., tables, 10 refs. Unclassified report</p> <p>The potentially toxic agent, 1,1-dimethylhydrazine (UDMH), has become very important from a medical viewpoint because of its large-scale use as a missile propellant. Pharmacological studies have revealed that the compound is primarily a central nervous system irritant, and latently causes cardiovascular collapse and ensuing irreversible shock. Pyridoxine therapy constitutes the first successful approach to</p> <p>(over)</p>	<p>UNCLASSIFIED</p> <ol style="list-style-type: none"> 1. Methyl Hydrazines 2. Toxicology 3. Vitamin B 4. Primates 5. Rodents 6. Dogs <ol style="list-style-type: none"> I. AFSC Project 6302, Task 630202 II. Biomedical Laboratory III. Back, K. C. IV. Pinkerton, Mildred K. V. Thomas, A.A. IV. In DDC collection V. Aval fr OTS: \$0.50 <p>UNCLASSIFIED</p>
<p>specific treatment which prevents convulsions and death in all species tested. The ED₅₀ (effective dose) of two vitamin B₆ congeners, pyridoxine hydrochloride and pyridoxamine dihydrochloride, was determined in mice, rats, dogs, and monkeys. The only manifestation which was not abolished by this therapy in dogs and monkeys was vomiting. The data presented in this paper are the basis for the suggested emergency treatment of severely exposed personnel, consisting of the injection of 25 mg/kg pyridoxine hydrochloride. The toxicity of pyridoxine, including overall therapeutic and clinical considerations with routes of administration, dosage regimens, and other supportive measures, is discussed.</p> <p>(over)</p>	<p>UNCLASSIFIED</p>	<p>specific treatment which prevents convulsions and death in all species tested. The ED₅₀ (effective dose) of two vitamin B₆ congeners, pyridoxine hydrochloride and pyridoxamine dihydrochloride, was determined in mice, rats, dogs, and monkeys. The only manifestation which was not abolished by this therapy in dogs and monkeys was vomiting. The data presented in this paper are the basis for the suggested emergency treatment of severely exposed personnel, consisting of the injection of 25 mg/kg pyridoxine hydrochloride. The toxicity of pyridoxine, including overall therapeutic and clinical considerations with routes of administration, dosage regimens, and other supportive measures, is discussed.</p> <p>(over)</p>	<p>UNCLASSIFIED</p> <p>UNCLASSIFIED</p> <p>UNCLASSIFIED</p>

FOREWORD

This work was performed in support of Project No. 6302, "Toxic Hazards of Propellants and Materials," Task No. 630202, "Pharmacology and Biochemistry," from November 1961 to March 1963 in the Toxic Hazards Branch, Physiology Division, Biomedical Laboratory. The valuable assistance rendered by Capt. D.B. Gisler, Capt. D.F. Dixon, and Capt. D. Ewing of the Veterinary Medical Section, and by Capt. A.B. Cooper and Miss Barbara Reynolds of the Toxic Hazards Branch is gratefully acknowledged. The authors also wish to thank Dr. R.L. Hamlin, Ohio State University, for his analysis of monkey vector cardiograms.

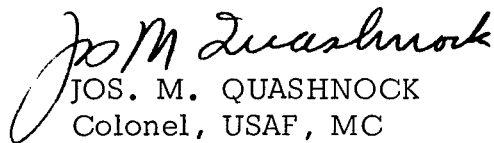
The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care," established by the National Society for Medical Research.

ABSTRACT

The potentially toxic agent, 1,1-dimethylhydrazine (UDMH), has become very important from a medical viewpoint because of its large-scale use as a missile propellant. Pharmacological studies have revealed that the compound is primarily a central nervous system irritant, and latently causes cardiovascular collapse and ensuing irreversible shock. Pyridoxine therapy constitutes the first successful approach to specific treatment which prevents convulsions and death in all species tested. The ED₅₀ (effective dose) of two vitamin B₆ congeners, pyridoxine hydrochloride and pyridoxamine dihydrochloride, was determined in mice, rats, dogs, and monkeys. The only manifestation which was not abolished by this therapy in dogs and monkeys was vomiting. The data presented in this paper are the basis for the suggested emergency treatment of severely exposed personnel, consisting of the injection of 25 mg/kg pyridoxine hydrochloride. The toxicity of pyridoxine, including overall therapeutic and clinical considerations with routes of administration, dosage regimens, and other supportive measures, is discussed.

PUBLICATION REVIEW

This technical documentary report has been reviewed and is approved.


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THERAPY OF ACUTE UDMH INTOXICATION

INTRODUCTION

The missile fuel, 1,1-dimethylhydrazine (UDMH), is being used on a large scale. Pharmacological studies have revealed that the compound is primarily a central nervous system irritant and causes latent cardiovascular collapse and ensuing irreversible shock when given in lethal doses (ref. 1). Consequently, there is an increasing medical interest in the clinical toxicology of this compound.

Early work indicated that certain hydrazine analogues produced inhibitory effects on enzyme systems intimately associated with production of gamma-aminobutyric acid and succinate (refs. 5,7). Some of these enzyme systems are dependent upon an active form of vitamin B₆ (pyridoxine) as a co-factor (ref. 8). This research led to the work of Dubnick, Leeson, and Scott (ref. 3) and Reeves (ref. 6) who reported that pyridoxine and pyridoxamine exhibited a protective effect in preventing seizures caused by specific hydrazine derivatives.

This report concerns both symptomatic and antidotal treatment of acute UDMH intoxication and especially the effects of two vitamin B₆ congeners, pyridoxine and pyridoxamine.

MATERIALS AND METHODS

All experiments were performed using Practical Grade UDMH obtained from Eastman Organic Chemicals, Rochester, New York; pyridoxine hydrochloride (PIN·HCl) obtained from Eastman Organic Chemicals; and pyridoxamine dihydrochloride (PAM·2HCl) obtained from Nutritional Biochemicals Corporation, Cleveland, Ohio. These chemicals were prepared for injection either in distilled water or in physiological saline.

The acute single dose 24-hour intraperitoneal toxicity of PAM·2HCl was determined in male Swiss albino mice. The statistical method used for computation of the LD₅₀ was that of Litchfield and Wilcoxon (ref. 4).

Male or female adult mongrel dogs were used to determine the effects of various sedatives, anticonvulsants, and vasoconstricting agents on the convulsive and cardiovascular effects of UDMH. All dogs were given 100 mg/kg UDMH by the i.p. or i.v. route and were treated symptomatically by a team of physicians, veterinarians, and pharmacologists in an effort to prevent death.

ED₅₀'s (effective doses against death from UDMH) for the vitamin B₆ congeners were determined in male Swiss albino mice and in male Sprague-Dawley rats. Rats and mice received 200 and 250 mg/kg UDMH i.p., respectively (2LD₅₀), followed by doses of either PIN·HCl or PAM·2HCl and the time of onset for convulsions and/or death was recorded. Observations were continued for 48 hours and the data were statistically analyzed (ref. 4).

Unanesthetized monkeys and dogs were given 100 mg/kg doses of UDMH, either i.v. or i.p., and observed for clinical signs such as nausea, vomiting, muscular fasciculation, and convulsions. PIN·HCl or PAM·2HCl was given by various routes, at various times, and at various dose levels, to evaluate the clinical effectiveness of the therapeutic agents. Monkeys were also used to determine the effects of UDMH and PIN·HCl on the ECG and blood pressure in the unanesthetized animal. Femoral blood pressure was recorded using a Model 5 Grass Polygraph and a Statham P23 AC pressure transducer attached to an indwelling catheter inserted under local anesthesia.

RESULTS

Toxicity of PIN·HCl and PAM·2HCl

The acute 24-hour LD₅₀ of PAM·2HCl in the mouse is 2100 (1533-2877) mg/kg i.p.; slope function, 1.44 (0.94-1.97). The LD₅₀ of PIN·HCl in rats as reported by Unna (ref. 9) is 370 mg/kg subcutaneously. The only reference in the literature to the LD₅₀ of PIN·HCl in mice is that of Weigand, Eckler, and Chen (ref. 10) who reported 545 mg/kg i.v. They also reported 657 mg/kg i.v. in rats. The toxic manifestations of both compounds were characterized by clonic and tonic convulsions, and death was attributed to respiratory arrest. These data imply that the two compounds are only slightly toxic.

Symptomatic Treatment of UDMH Toxicity

Seven dogs were given 100 mg/kg doses of UDMH either by the i.p. or i.v. route. All animals vomited in from 30 to 60 minutes and showed clonic and tonic convulsions in from 30 to 120 minutes. Pentobarbital, methitural, phenobarbital, and amobarbital failed either to control seizures adequately or to prevent death in any of the animals. Barbiturates only delayed the appearance of convulsions when given immediately following emesis and, in fact, appeared to enhance the depressant characteristics of UDMH toxicity. In anesthetic doses, they decreased the already depressed respiration. Diphenylhydantoin, an anticonvulsant, also failed to control convulsions and prevent death.

Those animals given only an anesthetic dose of barbiturate to control convulsant activity died of respiratory arrest. In some of the experiments, the dogs were given heroic treatment which included artificial respiration at the earliest signs of respiratory distress and meticulous nursing care. Despite anticonvulsant or anesthetic therapy, these animals continued to decline rapidly. After 2 to 4 hours, the cardiovascular system began to fail, and irreversible shock ensued. The shock was not ameliorated by potent vasoconstrictors such as norepinephrine, nor did infusion of blood or plasma expanders help, and the animals died in from 4 to 7 hours after UDMH administration. Death in these cases was preceded by cardiac decompensation which was not alleviated by the use of cardiac glycosides.

Effective Dose of PIN·HCl and PAM·2HCl in Rats and Mice

In the mouse the ED_{50} of PIN·HCl against $2LD_{50}$'s of UDMH as shown in figure 1 is 38 (32-46) mg/kg; slope function, 1.64 (1.34-1.97). The ED_{50} of PAM·2HCl is 62 (50-78) mg/kg; slope function, 1.76 (1.31-2.36). When the data are evaluated in terms of the free base (PIN and PAM), there is no significant difference between the two agents in their ability to prevent death in mice. Figure 1 also shows the relative abilities of the two compounds to protect against UDMH lethality in mice. Of importance is the fact that an erratic dose-response curve was obtained when PAM·2HCl was given at doses above 100 mg/kg. Analysis of table 1 indicates that, when convulsions were considered as the criterion rather than death, it was not possible to obtain a linear dose-response with PAM·2HCl. The ED_{50} for PIN·HCl against convulsions in the mouse is 75 (65-87) mg/kg; slope function, 1.72 (1.47-2.09).

In the rat, the ED_{50} of PIN·HCl against $2LD_{50}$'s UDMH is approximately 100 mg/kg, as shown in figure 2. This ED_{50} is an approximation because there is no straight line relationship between dose and effect. For PAM·2HCl, the ED_{50} was extrapolated to approximately 10 mg/kg. In rats, PAM·2HCl was nearly 10 times more potent than PIN·HCl. Again, table 1 indicates that protection against convulsions, at all dose levels, was erratic with both agents and was not predictable.

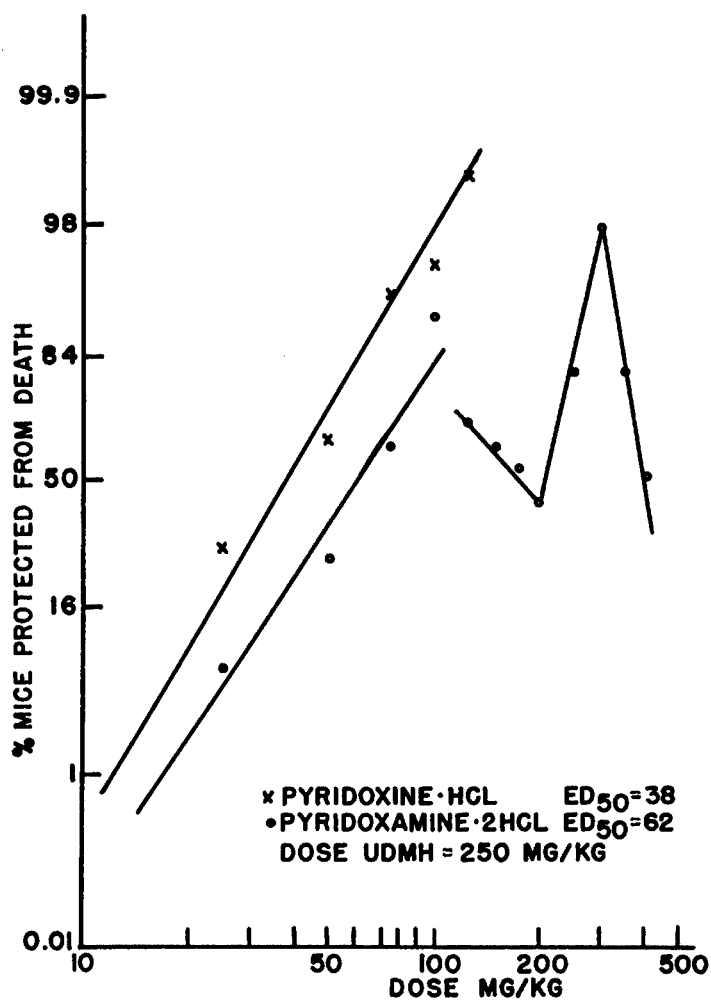


Figure 1. Antidotal Effectiveness of B₆ Analogues against UDMH in the Mouse

TABLE 1
 THE PROTECTIVE EFFECT OF PIN AND PAM AGAINST
 2LD₅₀ OF UDMH IN RATS (200 mg/kg)
 AND MICE (250 mg/kg)

DOSE MG/KG		RAT				MOUSE			
PIN	PAM	PIN		PAM		PIN		PAM	
		CONV	DEATH	CONV	DEATH	CONV	DEATH	CONV	DEATH
25	25	14/15	10/15	14/15	3/15	29/30	21/30	14/15	14/15
50	50			7/15	1/15	27/30	11/30	13/15	11/15
75	75	14/15	9/15	12/15	2/15	15/30	2/30	29/30	12/30
100	100	15/15	7/15	17/28	1/28	18/45	2/45	23/30	3/30
125	125					0/30	0/30	9/15	5/15
150	150	7/15	4/15	1/15	0/15	0/30	0/30	12/15	6/15
175	175							11/15	7/15
200	200	0/15	0/15					11/12	7/12
	250							2/10	2/10
	300							1/11	0/11
	350							5/10	2/10
	400							6/10	5/10

PIN = PYRIDOXINE·HCL
 PAM = PYRIDOXAMINE·2HCL

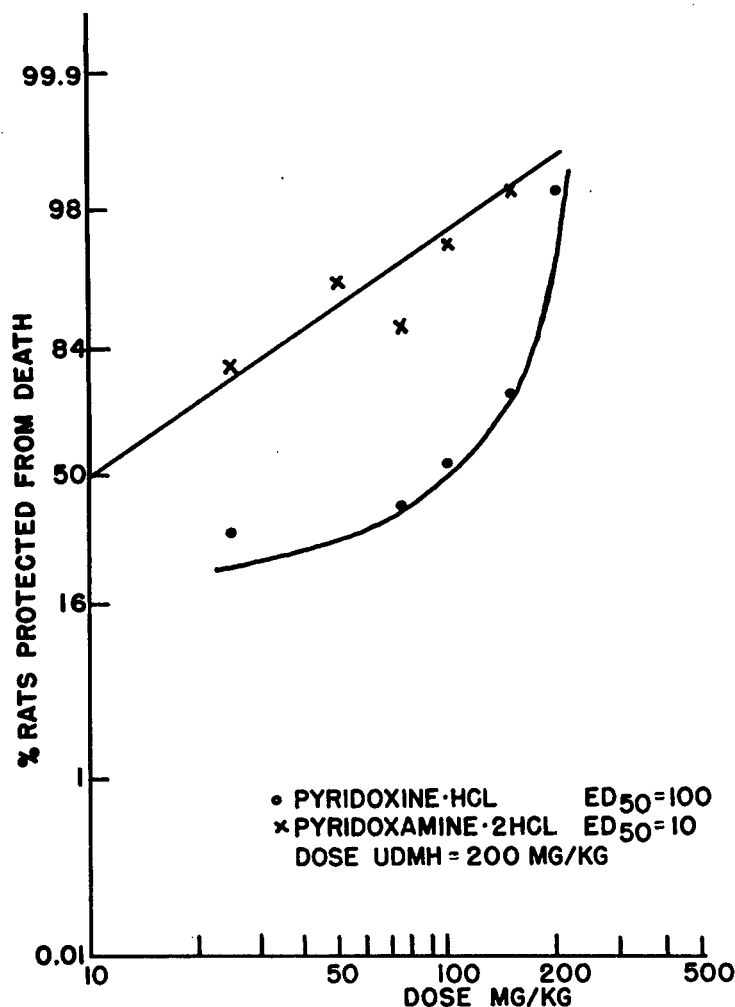


Figure 2. Antidotal Effectiveness of B_6 Analogues against UDMH in the Rat

Effective Dose of PIN·HCl in Dogs and Monkeys

In these experiments the animals were given a lethal dose (100 mg/kg) of UDMH i.v. PIN·HCl was given either subcutaneously or intramuscularly from 1 to 30 minutes after UDMH administration. The results are compiled in table 2.

In the dog, the dose of PIN·HCl necessary to protect most of the animals from death was between 100 and 150 mg/kg. The ED_{50} was approximately 100 mg/kg. The effective dose necessary to prevent convulsions was about 150 mg/kg. PIN·HCl did not protect against nausea and emesis in the dog.

TABLE 2

THE EFFECT OF PYRIDOXINE AGAINST A LETHAL DOSE OF UDMH (100 mg/kg)

ANIMAL	PYRIDOXAMINE MG/KG	EMESIS	CONVULSION
MONKEY	200	5/11	3/11
MONKEY	100	4/6	5/6
MONKEY	50	0/3	2/3
MONKEY	25	1/3	3/3

ALL MONKEYS THAT CONVULSED WERE GIVEN A DOSE OF PYRIDOXINE (25 MG/KG) TO INSURE SURVIVAL.

In the monkey the ED_{50} of PIN·HCl against death appeared to be approximately 25 mg/kg although no monkeys were allowed to die. Five of the nine animals convulsed at that dose, and some undoubtedly would have died if a second dose of 25 mg/kg had not been given. The dose of 50 mg/kg PIN·HCl protected all 19 monkeys against either convulsions or death. Emesis was not significantly affected, although it was more difficult to produce emesis in the monkey than in the dog. At 100 mg/kg UDMH, only 44% of the monkeys had emetic episodes while all of the dogs vomited.

Experience with Treatment of Convulsing Cats, Dogs, and Monkeys with PIN·HCl

This experience was gathered from concurrent pharmacological and biochemical experiments involving high doses of UDMH, where convulsive seizures occurred in the animals under study. These seizures were promptly arrested by administration of from 25 to 100 mg/kg PIN·HCl. In toto, 5 monkeys, 6 dogs, and 13 cats received doses of UDMH ranging from 50 to 100 mg/kg. Route of administration was either i.v. or i.m. Convulsions were completely abolished within 15 minutes. None of the animals died from UDMH exposure.

Effective Dose of PAM·2HCl in the Monkey

The monkeys used in these experiments were given 100 mg/kg UDMH i.v. The approximate ED_{50} against convulsions was extrapolated to 150 mg/kg (table 3). All monkeys that convulsed were given a dose of 25 mg/kg PIN·HCl to insure survival. Therefore, we did not determine the ED_{50} against death.

Cardiovascular and ECG Effects of UDMH and PIN·HCl in the Unanesthetized Monkey

Nine monkeys were used in this study. Blood pressure and standard electrocardiograms were recorded continuously throughout a $2\frac{1}{2}$ -hour period. Control tracings were taken for one-half hour, prior to the administration of 100 mg/kg UDMH i.p. PIN·HCl (50 mg/kg i.p.) was given 30 minutes later. Blood pressure in these animals routinely rose from 10 to 20 mm Hg after UDMH administration and remained elevated for from 15 to 30 minutes. ECG patterns did not change from normal after UDMH administration in any of the monkeys. The administration of PIN·HCl at this dose level did not appear to affect the blood pressure or ECG activity. All monkeys were returned to their cages after the experiment, and they recuperated with no untoward effects. Two weeks after the first experiment, each animal was returned for ECG evaluation and vector cardiographic analysis. Again, these were interpreted to be normal, and no latent effects were noted. All animals were still alive and healthy 4 months later.

TABLE 3

THE EFFECT OF PYRIDOXAMINE AGAINST A LETHAL DOSE OF UDMH (100 mg/kg)

ANIMAL	PYRIDOXINE MG/KG ROUTE	EMESIS	CONVULSION	DEATH
DOG	200 s.c.	3/3	0/3	0/3
DOG	150 s.c.	3/3	0/3	0/3
DOG	100 i.m.	9/9	3/9	2/9
DOG	2x50 i.m.	3/3	3/3	0/3
DOG	50 i.m.	3/3	3/3	2/3
MONKEY	100 i.m.	2/3	0/3	0/3
MONKEY	50 i.m.	8/19	0/19	0/19
MONKEY	25* i.m.	4/9	5/9	0/9

* WITH THE EXCEPTION OF ONE ANIMAL, ALL CONVULSING MONKEYS RECEIVED A SECOND DOSE OF 25 MG/KG PYRIDOXINE

DISCUSSION

These experiments have pointed out an extremely important species difference in the protective efficacy of PIN·HCl and PAM·2HCl against UDMH toxicity in laboratory animals. From our data, it appears that the mouse and the monkey are more easily protected by PIN·HCl than by PAM·2HCl. On the other hand, PAM·2HCl is approximately ten times more effective than PIN·HCl in the rat. These differences are probably caused by species differences in the metabolism of B₆ analogues. From a practical standpoint, both PIN·HCl and PAM·2HCl did afford protection in all species though the dose required for protection varied with the species. Either compound could probably be used therapeutically in man if the dose is properly adjusted. However, it is our opinion that for human treatment the agent of choice must be PIN·HCl. There are two reasons for this choice. First, PIN·HCl is the better agent when used to combat toxicity of UDMH in the phylogenetically higher order primate, and it will abort convulsions even after they have already begun. Second, this drug has been used as a therapeutic agent for years and can be obtained from drug sources in 200 mg/cc vials, ready for injection, whereas PAM·2HCl is not available for medical use. Intravenous injection of 200-mg doses of PIN·HCl in man with no untoward effects has been reported by Weigand, Eckler, and Chen (ref. 10). They also reported intramuscular injections of 50-mg doses with no lasting effects other than local soreness for from 1 to 2 hours.

In consideration of these data and our extensive experience with the pharmacology and toxicology of UDMH, it is our recommendation that the following regimen be used if personnel suffer severe exposure to UDMH.

The first sign of significant toxicity is emesis. There is sufficient time to abort convulsions even after the patient has vomited. Since extremely sensitive persons might develop nausea simply from the odor of UDMH, the circumstances of accidental exposure should be thoroughly explored before therapy is instituted.

If the probability of exposure is high and the patient displays nausea and/or vomiting, 25 mg/kg PIN·HCl should be given. In a 70-kg man this would be a total dose of 1750 mg, or about 8 cc. Two vials of injectable material may be given intravenously and the remaining vials intramuscularly in several areas. In the event the patient convulses in spite of this dose, a second dose of 25 mg/kg is indicated and should be given unless the convulsion is mild and fleeting. Of further therapeutic use would be hydration of the patient. We have shown that from 30% to 50% of UDMH is excreted in the urine in from 5 to 6 hours if an animal is given large amounts of fluid (ref. 2).

We must emphasize that there is no precedent for this therapy, and we know of no actual human exposures that were so severe as to cause convulsions. Still, this treatment can be justified in an emergency and is indeed the only known effective antidote. The use of hypnotics or barbiturates is probably contraindicated since data presented here and elsewhere (ref. 1) indicate that these drugs tend to decrease an already depressed respiration.

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